REMARKS

Applicants respectfully request reconsideration of this application in view of the above Amendment and the following remarks.

The Examiners has made FINAL the restriction requirement of January 11, 2006. Additionally, the Examiner has withdrawn Claims 12-14, 31-33, 49-51, 63, 69, 75, 77, 79, 80, 86, 88, 89, 97, and 99, as being drawn to a non-elected invention.

Claims 1, 11, 20, 30, 39, 44, 48, and 57 have been amended;

Claims 5, 6, 24, 25, 46, and 58-99 have been either canceled or withdrawn;

Claims 1-4, 7-9, 11, 15-20, 22, 23, 26-28, 30, 34-45, 47, 48, and 52-57 are under consideration in this response.

The amended claims find support in the specification in paragraphs: [0003-0009]; [0013-0015]; [0077]; [0085]; [0106]; [0126-0131]; [0151-0158]; [0162-0167]; Table 2; Figures 1, 2, and 5; and the original claims.

I. Rejections Withdrawn

Applicants acknowledge that the Examiner has withdrawn the rejections under 35 U.S.C. §102 and §103 over Schwartz et al., (U.S. Patent 6,423,693), in view of Applicants' amendments and election of SEQ ID No.: 1.

II. Specification

Applicants have amended paragraph, [0010] and [0167] to indicate the issuance of Application No. 09/624,268 as U.S. Patent 6,551,996, as recommended by the Examiner.

III. Claim Rejections – 35 USC §112, second paragraph

The Examiner is of the opinion that Claims 11, 30, 48, 62, 68, and 74 are indefinite because it is not clear if the claim phrase "a HV-GHRH plasmid (SEQ ID No: 11)" is to be interpreted broadly as any plasmid comprising a sequence encoding HV-GHRH, wherein SEQ ID No: 11 is an example of such a plasmid, or whether the claim is intended to be limited to SEQID No: 11.

In response, Applicants have amended Claims 11, 30, and 48 to remove the phrase a "HV-GHRH plasmid," the other claims have been canceled, which renders the Examiner's rejections moot.

IV. Claim Rejections – 35 USC §112, first paragraph

The Examiner has rejected Claims 1-9, 11, 15-20, 22-28, 30, 34-38, 40-47 and 52-57 for containing subject matter that was not described in the specification in such a way as to reasonably convey that Applicants had possession of the claimed invention. More specifically, the Examiner has stated that the claimed encoded polypeptide is *"limited only by function and not structure."* The Examiner has highlighted a peptide called ghrelin, which has no significant sequence similarities with GHRH, but has a similar function that is capable of causing secretion of growth hormone. The Examiner is of the opinion that the scope of the original claims includes polypeptides, such as ghrelin, whereas the specification only discloses specific forms of GHRH that vary at positions 1, 2, 15, 17, and 28, as illustrated in SEQID No.: 6. The Examiner has stated that Applicants' specification disclosed 48 modified forms of GHRH, and a wide variety of GHRH's from various species including human, bovine, porcine, ovine, rat, mouse, and chicken.

The Examiner has further rejected Claims 1-9, 11, 15-20, 22-28, 30, 34-48, 52-57 as being drawn to a genus of synthetic muscle-specific promoters, whereas the specification discloses only two examples of this genus.

In response, Applicants have amended independent Claims 1, 23, and 44 on which the other claims depend. The claims, as amended, contain the structural limitation that the isolated nucleic acid encodes a GHRH having at least 95% identity to SEQID No.: 1. Applicants have further limited Claims 20, 39, and 57 to specific amino substitutions of SEQ ID No.: 1 at positions 1, 2, 15, 17, and 28, as illustrated in SEQID No.: 6. These amendments are supported in the specification as indicated by the Examiner's statements in the Office Action.

Applicants have also included the limitation of structural conformation of the encoded GHRH to be capable of binding to a GHRH receptor. Applicants submit that support for the structure/function relationship of the physiologically relevant pathways regulating GHRH would be known by one of ordinary skill in the art, as described in the specification. More specifically, the specification describes the GHRH sequence functions in paragraphs [0003]-[0014] titled *"Growth Hormone Releasing Hormone ("GHRH") and Growth Hormone ("GH") Axis."* This section of the specification cited many publications and patents (specifically **incorporated by reference**, *see* pages 79-89 of the specification) describing the mechanisms and understanding of the GRHR/GH axis, including GHRH receptors at the time of the invention. Applicants submit that inclusion of the structural limitation of GHRH having at least 95% identity to SEQID No.: 1 renders moot the Examiner's example of ghrelin-like sequences having the genus of nucleic acid constructs encoding GHRH or functional biological equivalents thereof of the claims, as amended. Additionally, Applicants respectfully submit that the presence of the structural limitation of SEQID No.: 1 and the functional discussion of this molecule in the specification, together with what have been incorporated by reference in the application, renders moot the Examiner's rejections.

Applicants have further amended Claims 1, 23, and 44 to include the limitation of an "operatively positioned arrangement" to indicate the structural limitations of the promoter, encoded gene and 3' untranslated region. Applicants submit that the specification has dedicated an entire section to the structural and functional limitations of promoters useful for driving expression for the encoded GHRH of this invention. For example, paragraphs [0123-00131] describe specific examples and references that were **incorporated by reference** to indicate which structures are required to confer tissue-specific activity of promoters governing expression of the encoded genes. In paragraph [0130] Applicants specifically stated that:

"The identity of tissue-specific promoters or elements, as well as assays to characterize their activity, is well known to those of skill in the art."

Additionally, the Examiner has stated that: *"The specification discloses two examples of this genus."* See Page 6, line 16 of the Office Action.

Applicants submit that one of ordinary skill in the relevant art understands that a genus of synthetic promoters capable of driving expression of the encoded GHRH in muscle tissue is within the spirit and scope of the claims. Furthermore, a promoter that is so structurally mutated from the examples in paragraphs [0123-0131] that cannot properly drive expression of the encoded GHRH molecule (under conditions that promote expression of the nucleotide sequence in the muscle tissue) would not be included in the scope of the claims.

Applicants submit that the Court has expressly held: "it is possible for a specification to enable the practice of an invention as broadly as it is claimed, and still not describe that invention." *In re DiLeone*, 168 U.S.P.Q. 592, 593 (C.C.P.A. 1971). As an example, the Court has held: "where the specification discusses only compound A and contains no broadening language of any kind. This might very well enable one skilled in the art to make and use compounds B and C; yet the class consisting of A, B, and C has not been described." *Id.* at 593 n.1.

Applicants submit that the specification discloses: (a) at least two specific structures of synthetic muscle specific promoters; (b) has cited references for identifying, and assaying tissue specific promoters; and (c) has used language to indicate that one of ordinary skill in the relevant art could "*obtain such promoter sequences from databases including the National Center for Biotechnology Information ("NCBI") GenBank database or the NCBI PubMed site. A skilled artisan is aware that these databases may be utilized to obtain sequences or relevant literature related to the present invention.*"

Thus, Applicants submit, one of ordinary skill in the art could make and use other tissue specific promoters (i.e. compounds B and C in the Court decision discussed above); without having each and every class of specific promoters being described (i.e. compounds A, B, and C as discussed by the Court decision above).

V. Claim Rejections – 35 USC §102(e)

The Examiner has rejected Claims 1-9, 11, 18-20, 22-28, 30, 37-48, 55-62, 65-68, and 71-74 as being anticipated by Schwartz et al. US Patent 6,551,996, ("the '996 Patent" or "Schwartz et al.") as evidenced by Aihara et al., (Nature Biotech 16; 867-870, 1998, "Aihara et al."). The Examiner is of the opinion that Schwartz et al. taught a method of injecting into muscle of a farm animal a plasmid vector encoding SEQ ID NO: 1 (HV-GHRH, and optimized protease resistant form of the GHRH) under control of a synthetic muscle specific promoter (SPc5-12), wherein the site of the injection was subsequently subjected to electroporation. The Examiner is further of the opinion that Schwartz et al. refers to the Aihara et al. which teaches a method of electroporating nucleic acids into muscle by inserting electrode needles into muscle such that they encompassed the site into which the DNA is injected.

The Examiner has held that although Schwartz is silent with respect to an involuntary cull and body condition score, however, Schwartz anticipates all of the claimed active method steps, so the functional effects of the claimed methods are considered to be **inherent** in the method steps taught by Schwartz.

In response, Applicants have amended independent Claims 1, 23, and 44, to include the limitation of *"applying a constant current electrical pulse to the plurality of needle electrodes."* Support for this amendment can be found in the specification under the section titled "Electroporation," paragraphs [0150]-[0158]. For example, paragraph [0156] discusses:

> *"Controlling the current flow between electrodes allows one to determine the relative heating of cells. Thus, it is the current that determines the subsequent effectiveness of any given pulsing protocol and not the voltage across the electrodes... Thus, controlling and maintaining the current in the tissue between two electrodes under a threshold will allow one to vary the pulse conditions, reduce cell heating, create less cell death, and incorporate macromolecules into cells more efficiently when compared to predetermined voltage pulses."*

Applicants respectfully submit that neither Schwartz et al. nor Aihara et al., references discloses a step of applying a constant current electrical pulse to the electrodes during electroporation. Thus, Schwartz et al., as evidenced by Aihara et al., cannot anticipate Claims 1-9, 11, 18-20, 22-28, 30, 37-48, 55-62, 65-68, and 71-74, because neither reference describes applying a **constant current** electrical pulse to the plurality of needle electrodes.

The Court has held that in order to anticipate, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991). When a claimed invention is not identically disclosed in a reference, and instead requires picking and choosing among a number of different options disclosed by the reference, then the reference does not anticipate. *Mendenhall v. Astec Industries, Inc.*, 13 U.S.P.Q.2d 1913, 1928 (Tenn. 1988), *aff'd*, 13 U.S.P.Q.2d 1956 (Fed. Cir. 1989).

Further, Applicants respectively traverse the Examiner's reasoning on anticipation and the Examiner's inherency rejections based on anticipation.

The law is clear that in order to anticipate, there must be no difference between the claimed invention and the reference disclosure, as viewed by person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 U.S.P.Q. 1001, 1010 (Fed. Cir. 1991). When a claimed invention is not identically disclosed in a reference, and instead requires picking and choosing among a number of different options disclosed by the reference, then the reference does not anticipate. *Mendenhall v. Astec Industries, Inc.*, 13 U.S.P.Q. 2d 1913, 1928 (Tenn. 1988), *aff'd,* 13 U.S.P.Q.2d 1956 (Fed. Cir. 1989).

In *International Nickel Co. v. Ford Motor Co.*, 119 U.S.P.Q. 72 (SDNY 1958), the Court held that, in determining anticipation, the focus is on the question of whether the unintended production of a product was **purely a matter of chance** (*i.e.* **was sporadic**) or was the **inevitable result** of the reference teaching. In *Continental Can Company USA, Inc. v. Monsanto Co.*, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991), the Federal Circuit held that anticipation under the inherency doctrine requires that the missing descriptive matter be "**necessarily present** in the thing described in the reference [Emphasis added]."

To establish anticipation through inherency, the claim limitation must be "**necessarily present**" within the cited reference. *See Crown Operations*, 62 U.S.P.Q.2d at 1923. The mere fact that a certain claim limitation *may* result from a given set of circumstances in a prior art reference is not sufficient. *See Rapoport v. Dement*, 59 U.S.P.Q.2d 1215, 1222 (Fed. Cir. 2001). In *Rapoport*, the alleged infringer, who was attempting to invalidate the patent, did not demonstrate that the claimed subject matter would "necessarily result" from the treatment given in the reference. *See id.* He only argued that the preferred treatment in the reference did not exclude the claimed subject matter. *See id.* The court upheld the BPAI's decision that the reference did not disclose the claimed subject matter and did not anticipate the claim. *See id.* at 1223.

Further, a prior art reference cannot inherently disclose a claim element, thereby anticipating that element, unless the prior art reference contains an **enabling disclosure**. Inherency may not be assumed based solely on similarities between the claimed invention and the prior art. *See Crown Operations Int'l Ltd. v. Solutia, Inc.*, 62 U.S.P.Q.2d 1917, 1923 (Fed. Cir. 2002). Although one of ordinary skill in the art is not required to recognize the inherency in the prior art, the Federal Circuit requires that the assertedly anticipating disclosure must enable the subject matter of the reference and thus of the patented invention without undue experimentation. *See Elan Pharmaceuticals, Inc. v. Mayo Foundation for Medical Education & Research*, 68 U.S.P.Q.2d 1373, 1374 (Fed. Cir. 2003). In other words, to serve as an anticipating reference, the reference must **enable** that which it is asserted to anticipate. *See id.* at 1375 – 76; *see also Toro Co. v. Deere & Co.*, 69 U.S.P.Q.2d 1584, 1590 (Fed. Cir. 2004) (reiterating that inherent anticipation by a prior-art embodiment is not possible unless that embodiment is itself sufficiently described and enabled).

Thus, in addition to the requirement of "necessarily present" within the cited reference, anticipation under the inherency doctrine also requires that the prior-art embodiment is (1) sufficiently described; and (2) enabled.

Applicants respectfully submit that the Examiner has used an impermissible hindsight picking and choosing, and that Schwartz et al. as evidenced by Aihara et al. cannot anticipate the pending claims under §102 inherency because the prior-art embodiment in Schwartz et al. and in Aihara et al. is NOT sufficiently described and is NOT enabled. Further, the unintended production of product is NOT the inevitable result of the teaching of the reference.

1. The Requirement of Impermissible Hindsight Picking and Choosing

Schwartz et al. is silent about using intramuscular electroporation to introduce a vector into an animal. The Examiner then replied upon the teaching of Aihara et al. to "fill in this gap" of intramuscular electroporation.

In order to come up with what is claimed here, the Examiner is selectively choosing the disclosure of intramuscular electroporation in Aihara et al., but ignoring its total teaching of

using a vector of IL-5 transgene controlled by a CAG promoter. In contrast, the present invention requires the case of a vector which is capable of expressing a GHRH or protein analog thereof. Here the Examiner is selectively choosing the teaching of Schwartz et al. of using SPc5-12 promoter, but ignoring the total teaching of Schwartz et al. in that the weight of the treated animals were increased. Unlike the present invention, Schwartz et al. did not make any selection of treating only female animals, nor describe or teach that effects are in fact on the treated subject's offspring, and NOT on the treated subject itself.

As discussed above, when a claimed invention is not identically disclosed in a reference, and instead requires picking and choosing among a number of different options disclosed by the reference, then the reference **does not anticipate**. *Mendenhall v. Astec Industries, Inc., id.*

2. The Claim Limitations are Not Necessarily Present Within the Cited Reference

The requirement of "applying a constant current electrical pulse to the plurality of needle electrodes" **is not necessarily present in the thing described in the references**. In fact, there is simply no mention or suggestion of the need of constant current electrical pulse in either of the cited references.

3. Embodiment in Cited Art is Not Sufficiently Described

The embodiment in either Schwartz et al. or Aihara et al. simply has no description of electroporation using constant electrical pulse.

Further, although Schwartz et al. teaches that the SPc5-12 promoter has greatly increased transcriptional potencies when compared to natural muscle-specific promoters, the impact of this property on the reducing culling in herd animals is not described.

As such, neither Schwartz et al. nor Aihara et al. includes all details necessary to invariably reproduce the currently claimed invention, and, therefore, even in combination, they cannot be used as a basis for anticipation under inherency.

4. Embodiment in Cited Art is Not Enabled

Since neither Schwartz et al. nor Aihara et al. even discloses or suggests the use of constant current electrical pulse, how can either, or both, references be enabling? Thus, embodiment of either Schwartz et al. or Aihara et al. is not an enabling disclosure.

Applicants therefore respectfully submit that none of the requirements for anticipation under inherency is present in either of the cited references, or in their combination. Moreover, hindsight selective choosing and picking are required to come up with the claimed invention.

VI. Claim Rejections – 35 USC §103(a)

The Examiner has rejected Claims 1, 15-17, 23, 26, 34-36, 44, 52-54, 58, 64, 66, 70, 72, and 76 as being unpatentable over Schwartz et al. in view of Fewell (U.S. Application 2003/0109478, "Fewell"). The Examiner is of the opinion that Schwartz et al. taught a method of injecting into muscle of a farm animal a plasmid vector encoding SEQ ID NO: 1 (HV-GHRH, and optimized protease resistant form of the GHRH) under control of a synthetic muscle specific promoter (SPc5-12), wherein the site of the injection was subsequently subjected to electroporation, as discussed above. The Examiner has conceded that Schwartz et al. did not teach a transfection facilitation polypeptide.

However, the Examiner held that Fewell teaches a method of improving delivery of a nucleic acid expression construct to muscle cells in vivo comprising introducing into the muscle a nucleic acid expression construct an poly-L-glutamate, and electroporating the muscle tissue using needle electrodes.

In response, Applicants have amended Claims 1, 23, and 44, to include the limitation of *"applying a constant current electrical pulse to the plurality of needle electrodes."* Applicants submit that neither Schwartz et al. nor Fewell teaches or describes the use of a polyanion in combination with a nucleic acid expression vector during constant current electroporation. Applicants submit that because the amended limitations were not present in the cited references, either singly or in combination, it would NOT have been obvious to one of ordinary skill in the art to make the claim limitations, as amended, as part of a routine optimization. For these

reasons, Claims 1, 15-17, 23, 26, 34-36, 44, and 52-54, are patentable over Schwartz et al., in view of Fewell.

VII. Double Patenting I

Claims 1-9, 18-20, 22-28, 37-47, 55-61, 65-67, and 71-73 stand rejected on the ground of non-statutory obviousness-type double patenting over Claims 21-23 of U.S. Patent No. 6,423,693 ("the '693 Patent") in view of Schwartz et al. The Examiner is of the opinion that the '693 Patent contain claims drawn to methods of delivering to muscle cells in vivo an expression vector encoding GHRH and having vectors comprising 5' and 3' UTR's for the purpose of livestock improvement. The Examiner has stated that the '693 Patent does not claim a synthetic muscle specific promoter, and has stated that Schwartz et al. teaches a method of injecting a plasmid vector encoding SEQ ID No.: 1 into an animal to improve growth performance. The Examiner is of the opinion that it would have been obvious to one of ordinary skill in the art to use the promoter of Schwartz et al. in the method of the '693 Patent.

In response, Applicants have amended Claims 1, 23, and 44, to include the limitation of *"applying a constant current electrical pulse to the plurality of needle electrodes."* Applicants submit that Schwartz et al., the '693 Application, or their combination, does not teach or suggest the use of an isolated nucleic acid encoding GHRH of SEQID No.: 1 in combination with constant current electroporation for the purpose of reducing an involuntary cull, improving a body condition score, or increasing milk production, as required in the amended claims.

As such, Applicants respectfully submit double patenting rejections are improper.

VIII. Double Patenting II

Claims 15-17, 34-36, 52-54, 64, 70, and 76 stand rejected on the ground of non-statutory obviousness-type double patenting over Claims 21-23 of the '693 Patent and Schwartz et al. in view of Fewell. The Examiner is of the opinion that the '693 Patent and Schwartz et al. teach methods of delivering to muscle cells in vivo an expression vector encoding GHRH and having vectors, as discussed above. The Examiner has stated that the '693 Patent and Schwartz et al. DO NOT teach a transfection facilitation polypeptide. However, the Examiner is of the opinion

that it would have been obvious to use the poly-L-glutamate of Fewell in order to obtain the reasonably expected improvement in delivery and expression.

Applicants have amended Claims 1, 23, and 44, to include the limitation of *"applying a constant current electrical pulse to the plurality of needle electrodes,"* which was NOT taught or suggested in any of the cited references. Applicants submit that Schwartz et al., the '693 Patent, and Fewell either singly or in combination does NOT teach or suggest the use of an isolated nucleic acid encoding GHRH of SEQID No.: 1 in combination with constant current electroporation and a transfection facilitation polypeptide.

Again, Applicants respectfully submit that the double patenting rejections here are improper.

Conclusion

Applicants respectfully submit that, in light of the foregoing Amendment and remarks, the amended claims are in condition for allowance. A Notice of Allowance is therefore respectfully requested for Claims 1-4, 7-9, 11, 15-20, 22, 23, 26-28, 30, 34-45, 47, 48, and 52-57.

If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,

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